REMARKS

Status of the claims and formal matters

Claims 14, 15, 19, and 25-27 are pending in the instant application. Claims 1-13, 16-18, and 20-24 had been previously cancelled. Claims 19, 25, and 26 are cancelled herein, as they depended in part from a subsequent claim. New claims 28-35 are added herein. New claims 28-30 correspond to previously pending (and herein cancelled) claims 19, 25, and 26. New claim 31 is supported in [0025] on page 6 and in [0037] on page 12 of WO 04/026299. New claim 32 is supported in [0013] on page 3 and in [0026] on page 7 of WO 04/026299. New claim 33 is supported in [0026] on page 7 of WO 04/026299. New claim 34 is supported in [0035] on page 11 of WO 04/026299. New claim 35 is supported in [[0036] on page 12 of WO 04/026299. No new matter has been added by the instant amendments.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are and were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103, or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the amendment presented herein should not give rise to any estoppel.

Claim rejections under 35 U.S.C. § 103

1. The Examiner has maintained his rejection of claims 14-15, 19, and 25-27 under 35 U.S.C. § 103(a) as being unpatentable over Chenard (EP 0900568 A2) in view of Skradski (*Epilepsia* 2000) in further view of Dursun, *et al.* (*Canadian Journal of Psychiatry* 2000). Applicant respectfully disagrees.

Chenard does not teach the use of all AMPA receptor antagonists in the manufacture of a medicament for treating dyskinesia associated with dopamine agonist therapy.

The Examiner states that "Chenard teaches the administration of AMPA receptor antagonists for the treatment of dyskinesia which results as a side effect of dopamine agonist therapy given as a therapeutic regimen for Parkinson's disease..." Again, Applicant respectfully disagrees.

The compounds of the general formula I described in pending claim 14 of the instant application are used to treat dyskinesia manifest as chorea or dystonia in a subject. Prior to the filing date of the application, anticonvulsant sulphamates used in the treatment of epileptic seizures, such as those of the general formula I (for example, topiramate), had also been found to demonstrate efficacy in the treatment of essential tremor. Both epilepsy and essential tremor constitute conditions entirely distinct from the dyskinesia contemplated for treatment in the instant application ([0020], [0022]-[0025]). Yet, unexpectedly, the inventors found that the compounds *do* display efficacy in reducing dyskinesias.

The Examiner relies upon Chenard to demonstrate that it was, at the time of filing of the instant application, already known in the art to employ AMPA receptor antagonists to treat dyskinesia. However, beyond its title "AMPA antagonists for the treatment of dyskinesias associated with dopamine agonist therapy" and similar sweeping statements throughout the reference itself, Chenard provides nothing substantive that shows or even implies that, indeed, AMPA receptor antagonists can be used to treat dyskinesia resulting from the use of dopamine agonist therapy.

The few examples provided in Chenard constitute prophetic examples, i.e., they describe experiments that have not been carried out. Both experiments – the first to evaluate the effect of compounds on AMPA receptor activation-induced $^{45}Ca^{2+}$ uptake in rat cerebellar granule cell cultures and the second to assess the efficacy of the compounds in the treatment of dyskinesias associated with dopamine agonist therapy in the treatment of Parkinson's disease in a rhesus monkey model -- represent standard experimental studies in use at the time of filing. Neither is demarcated with any detail as to how the experimental parameters might be changed to test the very lengthy list of compounds contemplated by Chenard, leaving the person of ordinary skill in the art with an undue amount of experimentation to actually test the compounds in question.

Chenard provides no data whatsoever; nor does the reference provide any reasoned technical explanation to convince the ordinarily skilled artisan that AMPA receptor antagonists can be used to successfully treat dyskinesia resulting from the use of dopamine agonist therapy. Indeed, Chenard teaches nothing substantive about AMPA receptor antagonists in general and dyskinesia beyond its repeated speculation.

Even if the person of ordinary skill in the art had, at the time of filing of the instant application, believed that Chenard was in possession of the invention as claimed therein (in

Chenard), i.e., "The use of a compound selected from groups (A), (B), (C), (D), (E), or (F) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating dyskinesia associated with dopamine agonist therapy, wherein groups (A), (B), (C), (D), (E), and (F) are defined as follows…", such person would not presume that Chenard was in possession of an invention as seemingly proposed by the Examiner, i.e., the use of any AMPA receptor antagonist in the manufacture of a medicament for treating dyskinesia associated with dopamine agonist therapy.

There is no enabling teaching in Chenard that compounds outside those in groups (A), (B), (C), (D), (E), and (F) are useful in the treatment of dyskinesia associated with dopamine agonist therapy. In this light, Applicant notes that, although the number of compounds speculated by Chenard for use in dyskinesia treatment is substantially large, the list of compounds does not include the compounds described in U.S. Patent Application No. 10/527,761, including, for example, topiramate. Furthermore, the compounds listed in Chenard have significant structural differences from the compounds of the present application. Therefore, one of ordinary skill in the art would not consider a compound claimed in the present application as a compound in group (A), (B), (C), (D), (E), or (F) and would, thus, not be taught to treat dyskinesia with Applicant's compounds.

Skradski does not teach that topiramate is an AMPA receptor antagonist.

Skradski describes a study evaluating "topiramate (TPM) antagonism of glutamate receptors activated by kainate." Skradski's mention of AMPA receptors are limited to conclusory statements to the effect that the results provided in the publication provide support/evidence for an antagonistic effect of topiramate (TPM) "on some types of…AMPA…and/or kainate receptors.", and open-ended statements such as "At the concentration used in this investigation, it is likely that both AMPA and kainate receptors are fully activated. This precludes any definitive conclusions about the particular receptor subtype blocked by TPM…" Indeed, the authors conclude the publication by suggesting that "Ongoing studies to identify the molecular site through which TPM exerts its effects on kainate-evoked currents will undoubtedly provide important information concerning…the mechanism of action of TPM…" In other words, Skradski does not provide the person of ordinary skill in the art with

any reasonable expectation as to whether or not topiramate exerts an antagonistic effect on AMPA receptors.

Gryder, *et al.*'s publication (2003 *J Neuroscience* 23(18):7069-7074), submitted herewith, reports on their investigation of the actions of topiramate on pharmacologically isolated synaptic responses mediated by AMPA and GluR5 kainate receptors. Gryder refers, in the introduction, to Skradski, reiterating that "…it was not possible in these studies to distinguish between the effects of topiramate on these" (AMPA and kainate) "two receptor types."

Gryder performed assays to determine the relative effect of topiramate on AMPA and kainate receptors and, subsequently, reported that topiramate selectively blocks the kainate receptor (last sentence of introduction). Although Gryder notes that topiramate does have a depressant action on synaptic responses predominantly mediated by AMPA receptors, it is *much* weaker than topiramate's selective inhibition of the component of the excitatory synaptic response in BLA principal neurons that is mediated by pharmacologically defined GluR5 kainate receptors (first paragraph of discussion). In fact, Gryder states that "This indicates that GluR5 kainate receptors are likely to be substantially blocked during topiramate therapy at clinically effective doses. In contrast, AMPA receptor responses are reduced much more modestly at these concentrations. This is not surprising because AMPA receptors are crucial for excitatory synaptic transmission throughout the CNS, and their blockade would be expected to produce dramatic neurobehavioral impairment, which does not occur with topiramate at therapeutic doses."

Gryder indicates that the mechanism of action of topiramate is predominantly mediated at kainate receptors (rather than at AMPA receptors), apparently going towards solving Skradski's question of whether topiramate's antagonistic effect is exerted upon kainate receptors or AMPA receptors. Having reviewed both publications, the person of ordinary skill in the art is left without any inclination to choose topiramate as an AMPA receptor antagonist, as the publications indicate that topiramate is a kainate receptor antagonist, rather than an effective AMPA receptor antagonist. In fact, it is likely that the ordinarily skilled artisan, having reviewed Skradski and Gryder, would specifically *not* choose topiramate as an AMPA receptor antagonist to be contemplated for some therapeutic use.

Thus, even if the ordinarily skilled artisan were to believe, based on Chenard, that AMPA receptor antagonists in general (i.e., outside of Chenard's compound groups A-F) can be

employed in the treatment of dyskinesia, said artisan would not be reasonably motivated to select topiramate as an AMPA receptor antagonist for testing within Chenard's speculated therapeutic use.

Dursun does not teach the treatment of a dyskinesia manifest as chorea or dystonia.

The Examiner states that "…one would be further encouraged that the employment of topiramate in the treatment of dyskinesia would be successful in light of the teachings of Dursun…Dursun teaches that topiramate is able to improve myoclonic jerks in the patient…" Applicant respectfully disagrees.

The instant claim is directed to a method of treating dyskinesia, wherein the dyskinesia is manifest as chorea or dystonia. Chorea and dystonia are distinct in neurological origin from myoclonus. They are also different phenomenologically, and they respond differently to pharmacological agents.

In particular, myoclonus (myoclonic jerks) describes paroxysmal, quick, lightning-like jerks (contractions) of a muscle or group of muscles akin to epilepsy or convulsions. Indeed, the rapid speed and brief duration of myoclonus are definitive for the disorder. In contrast, chorea is characterized by slow, sinuous writhing and dance-like movements that start in one part of the body and move abruptly, unpredictably, and, often, continuously to another part. In fact, the movements in chorea may merge imperceptibly into purposeful or semi-purposeful acts. Dystonic movements are associated with prolonged bursts of electrical activity in affected muscle(s), causing sustained abnormal postures and bodily contortions.

The underlying neuronal mechanisms of myoclonus are different from the mechanisms underlying the chorea and dystonia referred to in the instant patent application. The primary mechanisms by which chorea and dystonia are produced are known and are different from the mechanisms underlying epileptic or convulsive activity. These fundamental differences can, for example, be borne out by the different responses observed to drug treatment. A pharmacological agent's efficacy for treating myoclonus has no predictive value in relation to its efficacy for treating chorea or dystonia.

Different types of movement disorders can develop, depending on the nature and location of damage to or malfunction of the central nervous system (brain and spinal cord), the nerves, and the muscles. For example, there can occur damage to the parts of the brain that control voluntary movement or the connections between the brain and spinal cord, resulting in weakness

or paralysis of the muscles involved in voluntary movements and exaggerated reflexes. There can also occur damage to the basal ganglia, resulting in involuntary or decreased movements. There can also occur damage to the cerebellum, resulting in loss of coordination. And for each of the above-mentioned occurrences of damage, there are distinct movement disorders that may come about as a result of a specific subtype of damage. Thus, the person of ordinary skill in the art would not assume that several movement disorders could, with a reasonable expectation of success, be treated with a single agent. More specifically, the ordinarily skilled artisan would not reasonably expect that a therapeutic agent (topiramate) used to reduce myoclonic jerks developed in a schizophrenic patient taking clozapine would be therapeutically effective against dyskinesia manifest as chorea or dystonia. Applicant also points out that topiramate was additionally selected for the treatment of the schizophrenic exhibiting severe myoclonus, because topiramate had also been previously observed to have weight loss and mood-stabilizing properties, both specifically beneficial to the patient at hand.

Thus, the combination of Chenard, Skradski (in view of Gryder), and Dursun does not provide an implicit motivation to, let alone an explicit teaching of, employ(ing) a compound as defined in the instantly pending claim 14 to treat dyskinesia manifest as chorea or dystonia. If an independent claim is non-obvious under 35 U.S.C. § 103, then any claim depending therefrom is non-obvious. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Having established the non-obviousness of claim 14, claims 15 and 27-35 are, by extension, also non-obvious. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

Should the Examiner be of the opinion that it would be helpful to submit an expert Declaration in support of Applicant's above-iterated argument regarding the non-obviousness of the claimed invention, Applicant would willingly comply.

CONCLUSION

Applicant requests a telephone Interview with the Examiner to discuss the instant Office Action response, should the Examiner believe such a conversation would be beneficial and could advance the prosecution of the application.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

/Marina Heusch/

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